## Remarks

The Office Action mailed July 15, 2003 has been received and reviewed. Claims 25, 30, 36, 41, 43, and 45 having been amended, and claim 51 having been added, claims 25-30 and 35-51 are pending. Reconsideration and withdrawal of the rejections are respectfully requested in view of these remarks and the remarks made in the response submitted April 28, 2003.

Support for the amendment of claims 25 and 36 to recite "improved ability to degrade atrazine and increased degradation of terbuthylazine" can be found at, for example, page 19, line 26 through page 20, line 15 and the paragraph spanning pages 21 and 22.

New claim 51 is supported by, for instance, originally filed claims 25 and 30.

### Information Disclosure Statement

The Examiner states that the Information Disclosure Statement submitted on August 23, 2002 is not in the application file. Applicants' representative contacted the Examiner by telephone on October 10, 2003, and were informed that the Examiner does have the Information Disclosure Statement, 1449 forms, and documents submitted on August 23, 2002.

Applicants request that a copy of the 1449 forms, marked as being considered and initialed by the Examiner, be returned with the next Official Communication. The Examiner is thanked for the courtesies extended to Applicants' representative during the telephone conversation.

It is Applicants' understanding that no fee will be required for consideration of the documents as they were submitted to the Office before the first Office Action was mailed. As evidence of this, Applicants have enclosed (as Exhibit A) a copy of the PTO date-stamped postcard indicating the Information Disclosure Statement was received in "Tech Center 1600/2900" on August 26, 2002. The Examiner is requested to contact the undersigned if a copy of the Information Disclosure Statement and the 1449 forms are required.

**Objection of the Specification**

The Action notes that Applicants amendment of the description of Figure 9 "indicates that the sequence identifier for Pseudomonas sp. Strain ADP is SEQ ID NO:16 and the sequence identifier for Clavibacter (Clav.) is SEQ ID NO:16." The Examiner is requested to note that the amino acid sequences shown in Figure 9 for Pseudomonas sp. Strain ADP and for Clavibacter (Clav.) are identical. For this reason, a single sequence identifier was used to describe both of the amino acid sequences. Reconsideration and withdrawal of the objection is respectfully requested in view of this explanation.

**Rejection under 35 U.S.C. §112, first paragraph (Written Description)**

The Examiner rejected claims 25-29, 35-40, 42-44, 46-48, and 50 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice . . . reduction to drawings . . . or by disclosure of relevant, identifying characteristics (MPEP 2163(II)(A)(3)(a). Applicants respectfully maintain that the claims comply with the written description requirement for those reasons stated in the response mailed April 28, 2003.

Applicants further submit that the written description requirement for the claims is satisfied by the sufficient description of a representative number of species. The present application teaches seven species having altered catalytic activity (referred to in the specification as A7, T7, A40, A42, A44, A46, and A60; see, for instance, the paragraph bridging pages 21 and 22). Each of these seven have an improved rate of catalytic activity for atrazine, and six of these (A7, T7, A42, A44, A46, and A60) also display an increased degradation of terbuthylazine.

Each of these species has been reduced to practice, and the nucleotide and amino acid sequences of each of these species is disclosed.

Independent claims 25 and 43 comply with the Written Description requirement. Claims 25 and 43 are drawn to method for using a genus of proteins, where each protein is encoded by nucleic acid sequence that hybridizes to one specific sequence under high stringency conditions. This genus of proteins must have a specific activity, i.e., an altered catalytic activity relative to the protein having the amino acid sequence of SEQ ID NO:2 wherein the altered catalytic activity is an improved ability to degrade atrazine or an increased degradation of terbuthylazine (claim 25) or an improved ability to degrade atrazine as compared to the protein having the amino acid sequence of SEQ ID NO:2 (claim 43). A person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims as the stringent hybridization conditions set forth in the claims yield DNAs with few differences in structure, and due to the degenerate nature of the genetic code many of these differences would not change the amino acid sequence of the protein encoded thereby. Hybridization of a nucleic acid to the specific nucleic acid sequence was a conventional technique at the time the present application was filed. A representative number of species is disclosed, since stringent hybridization conditions in combination with the specific activity of the proteins encoded by the nucleic acids and the level of skill in the art are adequate to determine that the Applicants were in possession of the claimed invention.

Independent claims 36 and 47 comply with the Written Description requirement. Claims 36 and 47 are each drawn to a method for using a genus of proteins having at least 95% identity to a specific amino acid sequence. This genus of proteins must be involved in a specific activity, i.e.,an altered catalytic activity relative to the protein having the amino acid sequence of SEQ ID NO:2 wherein the altered catalytic activity is an improved ability to degrade atrazine or an increased degradation of terbuthylazine (claim 36) or an improved ability to degrade atrazine as compared to the protein having the amino acid sequence of SEQ ID NO:2 (claim 47). A person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims as all the proteins must possess the specific activity and must have

at 95% identity to SEQ ID NO:2. The seven species disclosed are representative of the genus as all members have at least 95% identity to SEQ ID NO:2 and all members must have the specific activity.

It is respectfully submitted that the pending claims comply with the written description requirement. Accordingly, the Examiner is requested to reconsider and withdraw the rejection of claims 25-29, 35-40, 42-44, 46-48, and 50 under 35 U.S.C. §112, first paragraph.

**Rejection under 35 U.S.C. §112, first paragraph (Enablement)**

The Examiner rejected claims 25-29, 35-40, 42-44, 46-48, and 50 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is respectfully traversed.

The Action states that the specification does not support the broad scope of the claims because it does not establish (a) regions of the protein which may be modified without effecting atrazine degrading activity, (b) the general tolerance of atrazine degrading enzymes to modification and the extent of such tolerance, (c) a rational and predictable scheme of modifying any amino acid of an atrazine degrading enzyme with an expectation of obtaining the desired atrazine catalytic activity, and (d) guidance as to which of the essentially infinite possible choices is likely to be successful (Action, page 9). The Action concludes that "[b]ecause of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the atrazine degrading activity while simultaneously altering this activity such as altering the catalytic rate" and the unpredictable relationship between the sequence of a peptide and its tertiary structure, "it would require undue experimentation for one skilled in the art to arrive at the majority of those methods of use of the claimed mutant atrazine degrading enzymes" (Action, sentence spanning pages 9-10).

Applicants respectfully submit that the requirements described at points a, b, c, and d on page 9 of the Action are not required by the statute, and Applicants are not aware of case law that includes such requirements. The standard for determining if a specification meets

the enablement requirement is whether the experimentation needed to practice the invention undue or unreasonable, and "even though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation" (MPEP 2164.01, emphasis added). Knowledge of which regions of the protein may or may not be changed is not necessary when making members of the genus of proteins encoded by a nucleic acid sequence that hybridizes or has the percent identity, and the specification provides ample direction and guidance for the skilled person to make proteins within the scope of the claims.

Furthermore, this enablement rejection is implicitly based on the premise that a person of skill in the art produces the enzymes within the scope of the claim by deciding which amino acid(s) will be altered in SEQ ID NO:2, making a protein containing those alterations, and then measuring the activity of the protein. This premise is false. Applicants agree that the skilled person *could* identify proteins falling within the scope of the claims by making them one at a time by, for instance, site directed mutagenesis, and screening them. Applicants also agree that knowledge of which amino acids are tolerant or intolerant to modification could make this type of experimental approach less time consuming. However, the skilled person can also use other methods that do not require any knowledge of where to make mutations. Such methods are taught in the working examples of the present specification, and others are disclosed at, for instance, the paragraph spanning pages 15-16 of the specification.

For at least these reasons, it is respectfully submitted that the requirement that the specification teach "(a) regions of the protein which may be modified without effecting atrazine degrading activity, (b) the general tolerance of atrazine degrading enzymes to modification and the extent of such tolerance, (c) a rational and predictable scheme of modifying any amino acid of an atrazine degrading enzyme with an expectation of obtaining the desired atrazine catalytic activity, and (d) guidance as to which of the essentially infinite possible choices is likely to be successful" (Action, page 9) is arbitrary because such knowledge is not needed by the skilled person to practice the invention.

The term 'undue experimentation,' has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation (MPEP 2164.01). It is respectfully submitted that the present invention can be practiced without undue experimentation. "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (citation omitted). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (citations omitted)" (In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The present specification provides working examples teaching how to use gene shuffling to randomly mutagenize the wild-type *atzA* coding sequence (SEQ ID NO:2) to make large numbers of nucleotide sequences encoding putative mutants of the *atzA* coding sequence (Example 2). The specification also provides working examples teaching how to use a routine screening method to identify nucleotide sequences encoding mutant enzymes having an improved ability to degrade atrazine compared to the wild-type AtzA enzyme (Example 2, paragraph spanning pages 27-28). The specification further teaches that the gene shuffling procedure can be repeated to obtain nucleotide sequences encoding mutant enzymes with even greater activity than those mutants identified in the first round of mutagenesis (Example 2, page 28, lines 3-7). Working example 6 teaches how nucleotide sequences encoding putative mutants of the *atzA* coding sequence having increased degradation of terbuthylazine are identified. These working examples provide ample direction and guidance allowing the skilled person to make the claimed enzymes.

The skilled person would not consider the quantity of experimentation necessary to practice the invention to be undue. As can be seen from working example 2, one experimental trial resulted in approximately 40 colonies that appeared to have increased activity (page 27, lines 29-33). The entire process was then repeated 4 times to further improve upon the rate of enzymatic activity (page 28, first full paragraph). As disclosed at the paragraph spanning pages

19 and 20 of the specification, this resulted in the identification of homologs having altered catalytic activity relative to the protein having the amino acid sequence of SEQ ID NO:2 wherein the altered catalytic activity is an improved ability to degrade atrazine or an increased degradation of terbuthylazine (claims 25 and 36) or an improved ability to degrade atrazine as compared to the protein having the amino acid sequence of SEQ ID NO:2 (claims 43 and 47). In this art, the use of screening methods to identify and select particular molecules of interest from a heterogenous population created by random laboratory procedures is standard practice, and those in the art are highly skilled in the use and evaluation of such screening procedures. Regarding the predictability or unpredictability of the art, "[T]he scope of the required enablement varies inversely with the degree of predictability involved" (MPEP 2164.03). It is Applicants' position that the detailed working examples contain the amount of direction and guidance to teach the skilled person how to make and use the claimed invention..

The first paragraph of §112 requires no more than a disclosure sufficient to enable the skilled worker to carry out the invention commensurate with the scope of the claims. It is respectfully submitted that upon reading Applicant's detailed specification the skilled worker would be able to carry out the invention commensurate with the scope of the claims. The Examiner is respectfully requested to reconsider and withdraw the rejection of claims 25-29, 35-40, 42-44, 46-48, and 50 under 37 C.F.R. §112, first paragraph.

## Summary

It is respectfully submitted that the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.



Respectfully submitted for
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DLP/skd

CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Commissioner for Patents, Mail Stop AF, P.O. Box 1450, Alexandria, VA 22313-1450, on this 15th day of October, 2003, at 4:35 pm (Central Time).

By: Sue Dombroske
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**Exhibit A**

**Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:**

Applicant(s): WACKETT et al.
Serial No.: 09/866,307
Filed: 25 May 2001
Title: DNA MOLECULES AND PROTEIN DISPLAYING IMPROVED TRIAZINE COMPOUND DEGRADING ABILITY



**Enclosed:** An Information Disclosure Statement (2 pgs); copy of International Search Report (7 pgs.); copies of 3 applications; 1449 forms (11 pgs); and copies of 123 documents cited on the 1449 forms; and transmittal document in triplicate

Mailed: August 23, 2002
Docket: 110.00440102

DLP/akd